Procter&Gamble

The Procter & Gamble Company
Winton Hill Technical Center
6071 Center Hill Avenue, Cincinnati, Ohio 45224-1703

March 3, 2000

Docket Management Office
5630 Fisher's Lane
Rockville, MD 20852

Dear Madam:

We wish to submit the enclosed report and cover letter entitled "The Olestra Post-marketing Surveillance Study: Findings from the First Year of Surveillance at the Sentinel Site, Indianapolis, IN 1996-1998" to the olestra docket #00F-0792 so that it is publicly available. All of this material has been previously submitted to Mary Ditto of FDA's Office of Pre-market Approval.

Please let me know if you have any questions (513-634-6808).

Thank you.

Sincerely,

THE PROCTER & GAMBLE COMPANY

Greg Allgood /lrd

Greg Allgood, Ph.D.
Associate Director
Regulatory & Clinical Development

Enclosure

00F-0792

RPT3

The Olestra Post-Marketing Surveillance Study:

Findings from the First Year of Surveillance at the Sentinel Site, Indianapolis, IN, 1996-1998

Prepared for the Food and Drug Administration

By

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April 15, 1998

The Olestra Post-Marketing Surveillance Study, Indianapolis, IN, 1996-1998

Executive Summary

Background and Specific Aims:

This report describes the objectives, design, methods, and results from the first year of sentinel site activity of the Olestra Post-Marketing Surveillance Study. Olestra is a calorie-free fat substitute approved by FDA in January, 1996 for use in savory snacks such as potato chips, tortilla chips, and cheese curls. The Procter & Gamble Company, the manufacturer of olestra, agreed to conduct post-market, active surveillance of olestra following its approval, in order to monitor olestra intake and serum nutrient status in the U.S. population.

Researchers at the Fred Hutchinson Cancer Research Center in Seattle, WA, designed and coordinated the post-market surveillance study. These researchers identified three specific aims to be addressed by the study:

(1) To monitor adoption and patterns of use of olestra-containing food products in representative samples of the U.S. population.

(2) To assess the association between the introduction of olestra-containing foods and serum concentrations of carotenoids and fat soluble vitamins in representative cross-sectional samples of the U.S. population.

(3) To assess the long-term association between consumption of olestra-containing foods and serum concentrations of carotenoids and fat soluble vitamins among a cohort of olestra consumers.

This study is being conducted in four cities: Indianapolis, IN; San Diego, CA; Minneapolis, MN; and Baltimore, MD. The Indianapolis site was designated the sentinel site, because data collection began in 1996, one year before the other three sites. Indianapolis was chosen for the sentinel site because it was the full scale test market in 1997. Data collection at the remaining three sites began in late 1997, prior to the nationwide release of olestra products in early 1998.

Data from a full year of activity at the sentinel site are now available, and are the basis of this report. The analyses given here are representative of those that will become available from the combined sites. Future analyses, based on all four sites combined, will be necessary to address the study hypotheses adequately. The results given here are preliminary, and because of the small numbers of participants, are not statistically reliable. It is important to note that the methods, results and conclusions described here apply only to the first year of study at the Indianapolis site.

Design and Methods:

This study has three components corresponding to the three specific aims:

Specific Aim 1. Two **telephone cross-sectional samples** were used to monitor the prevalence and patterns of olestra snack consumption. The first random-digit-dial telephone survey of Marion County, IN, residents was completed between August, 1996, and December, 1996, before the release of olestra snacks in February, 1997. The second random-digit-dial survey was completed between August, 1997, and January, 1998. The first (Year 0) survey included 2,179 adults age 18 year and over, and the Year 1 survey included 1, 549 adults. Conservatively-estimated efficacy (response) rates were 64.2% at Year 0 and 60.9% at Year 1. Complete data were available for analyses from 1,962 adults at Year 0 and 1,525 adults at Year 1. The survey collected information on diet (fruit and vegetable consumption and savory snack food consumption) and demographic characteristics.

Specific Aim 2. Two **clinic cross-section samples** were used to assess associations of olestra intake with serum concentrations of fat-soluble vitamins and carotenoids in representative samples of the population. A random sample of participants in each telephone cross-section sample were recruited into the two clinic cross-sections. There were 1,069 adults in the clinic cross-section at Year 0 and 947 at Year 1. Sufficient data were available for analysis from 1,043 adults at Year 0 and 934 adults at Year 1. Data collected at the clinic visit included comprehensive information on dietary intake, information on health-related behavior, other factors related to serum nutrient concentration, and a fasting blood sample for analysis of serum lipids, fat-soluble vitamins, and carotenoids.

Specific Aim 3. A **clinic cohort sample** was used to assess associations of olestra intake and *changes* in serum concentrations of fat-soluble vitamins and carotenoids. The cohort was recruited from participants in the Year 0 clinic cross-section. Cohort participants were selected based on olestra intake reported during three follow-up telephone interviews, completed approximately every three months after the Year 0 visit. There were 402 non-pregnant, adult participants in the cohort with sufficient data for analysis. Eighty percent of the participants in the cohort reported the highest intakes of olestra during the follow-up calls and 20% reported no intake of olestra. Cohort participants completed a Year 1 clinic visit. Data collection included comprehensive information on dietary intake, information on health-related behavior and other factors related to serum nutrient concentration, and a fasting blood sample for analysis of serum lipids, fat-soluble vitamins, and carotenoids.

Clinic cross-section and cohort participants also gave data on gastrointestinal symptoms and other health-related factors. These data and analyses of their relationships to olestra intake are not included here, but will be provided in future reports.

Results and Discussion:

Specific Aim 1. Olestra Intake: Based on the Year 1 telephone cross-section data that were weighted to be representative of the Marion County, IN, population, 15.5% of adults reported eating olestra-containing savory snacks *one or more times per month*. Based on more detailed dietary assessment in the clinic cross-section, 23% of adults reported *any* consumption of olestra snacks in the previous month. Among adult olestra snack eaters, the population-weighted median consumption was 1.2 servings or 8.1 grams of olestra per month (Table 1). The 90th percentile of olestra consumption was 9.2 servings or 64.4 grams of olestra per month. There were not enough children in the sample to make meaningful estimates about olestra consumption in that subgroup.

Intake of fruits and vegetables, and intake of total snacks, did not change in the population cross-section between Year 0 and Year 1. Olestra snack introduction was therefore not associated with an overall increase in savory snack consumption, nor was olestra snack introduction associated with a decrease in fruit and vegetable intakes. There was a modest decrease in consumption of reduced- and non-fat savory snacks at Year 1, suggesting that olestra snacks were being substituted for other low-fat snacks.

Specific Aim 2. Olestra intake and nutrient status in the population: There were no statistically significant decreases in population-weighted mean serum carotenoid or fat-soluble vitamin concentrations between Year 0 and Year 1. There were significantly higher concentrations of Vitamin E and β-cryptoxanthin. There was a significantly lower percentage of energy consumed from fat associated with increasing olestra consumption. Tests of associations of olestra consumption and serum concentrations of fat-soluble vitamins and carotenoids were based on regression models developed using data collected at Year 0, before olestra was consumed. The same variables used to predict serum concentration in Year 0 were used with Year 1 data, with the addition of variables to characterize four levels of olestra use: 0 g/day, >0 - 0.4 g/day, >0.4 - 2.0 g/day and >2.0 g/day. These cut points (0.4 and 2.0 g/day) correspond to the 50^{th} and 90^{th} percentile of olestra intake among adult olestra consumers in the clinic cross-section at Year 1. The numbers of adults in these four groups were 679, 129, 62 and 26, respectively.

There were no statistically significant associations between olestra intake and serum concentrations of retinol, 25-OH vitamin D, α-tocopherol, or total carotenoids (Figure 1A). There was a significant positive trend (p=0.01) in serum Vitamin K (phylloquinone) with increasing olestra intake. There were no statistically significant associations between olestra intake and serum concentrations of α-carotene, β-carotene, lycopene, lutein, zeaxanthin, or β-cryptoxanthin (Figure 1B). There were no consistent dose-response trends for increasing or decreasing concentrations of any serum carotenoid with increasing intake of olestra.

There were only 86 children below age 18, which is an insufficient sample size to do meaningful modeling of the association between olestra intake and serum nutrients. Twenty-five percent of the children in the clinic cross-section reported eating an olestra containing snack in the previous month.

Specific Aim 3. Olestra intake and serum nutrients in the cohort: Between Year 0 and Year 1 among all cohort participants, there were unexplained statistically significant decreases in mean serum concentrations of retinol, 25-OH vitamin D, total carotenoids, lycopene, lutein, and zeaxanthin, and increases in β-cryptoxanthin. There was a significant trend for reduced percentage of energy from fat with increasing olestra intake. Tests of associations between olestra consumption and changes in serum concentrations of fat-soluble vitamins and carotenoids were based on regression models that included variables to characterize the four levels of olestra use defined in cross-section analysis: 0 g/day, >0 - 0.4 g/day, >0.4 - 2.0 g/day and >2.0 g/day. The numbers of persons in these four groups were 248, 73, 46, 20 respectively.

There were no statistically significant associations between olestra intake and changes in serum concentrations of retinol, 25-OH vitamin D, α-tocopherol, vitamin K or total carotenoids. (Figure 2A), or between olestra intake and changes in serum concentrations of α-carotene, β-carotene, lycopene, lutein, zeaxanthin, or β-cryptoxanthin (Figure 2B). There were no consistent dose-response trends between olestra consumption and changes in individual carotenoids. Unlike findings in the clinic cross-section, the trend for increased serum Vitamin K with increased olestra intake was not statistically significant.

Overall conclusions:

The first year of active surveillance of olestra snack use has been successfully completed in the Indianapolis sentinel site. The design and methods developed and tested have been implemented in three additional large cities in the U.S., which will provide ongoing information about olestra use and its association with measures of nutritional status. Because the sample size in this preliminary analysis from the sentinel site is small, the analyses presented here could not detect changes in concentrations of serum nutrients that were smaller than 20%. The full national study and the repeated cohort measures will provide adequate power to address the objectives set out in the specific aims of this surveillance study.

Based on the initial year of observation in the Indianapolis site, estimates of olestra intake were low and well below pre-market projections. Based on the limited numbers of olestra consumers identified in the first year of this study, there were no consistent trends or statistically significant associations between olestra consumption and serum concentrations of fat-soluble vitamins or carotenoids.

Table 1. Olestra Consumption among Indianapolis Clinic Cross-Section Adult Participants at Year 1, adjusted to be Representative of the Marion County population. Olestra Post-Marketing Surveillance Study, Indianapolis, IN, 1996-1998.

	Consumption Among Olestra Users (n = 217)[1] Percentiles				
	10	25	50	75	90
Olestra Use					
Frequency/Month	0.3	0.4	0.9	2.3	4.7
One Ounce Snack Servings/Month	0.3	0.5	1.2	3.9	9.2
Grams/Month	1.7	3.6	8.1	26.9	64.4

[1] Of the 933 adults in the clinic cross-section, 217 (23%) reported olestra snack consumption in the month prior to the clinic visit. Frequency/month can be less than 1 due to adjustment procedures used in analyzing food frequency questionnaires.

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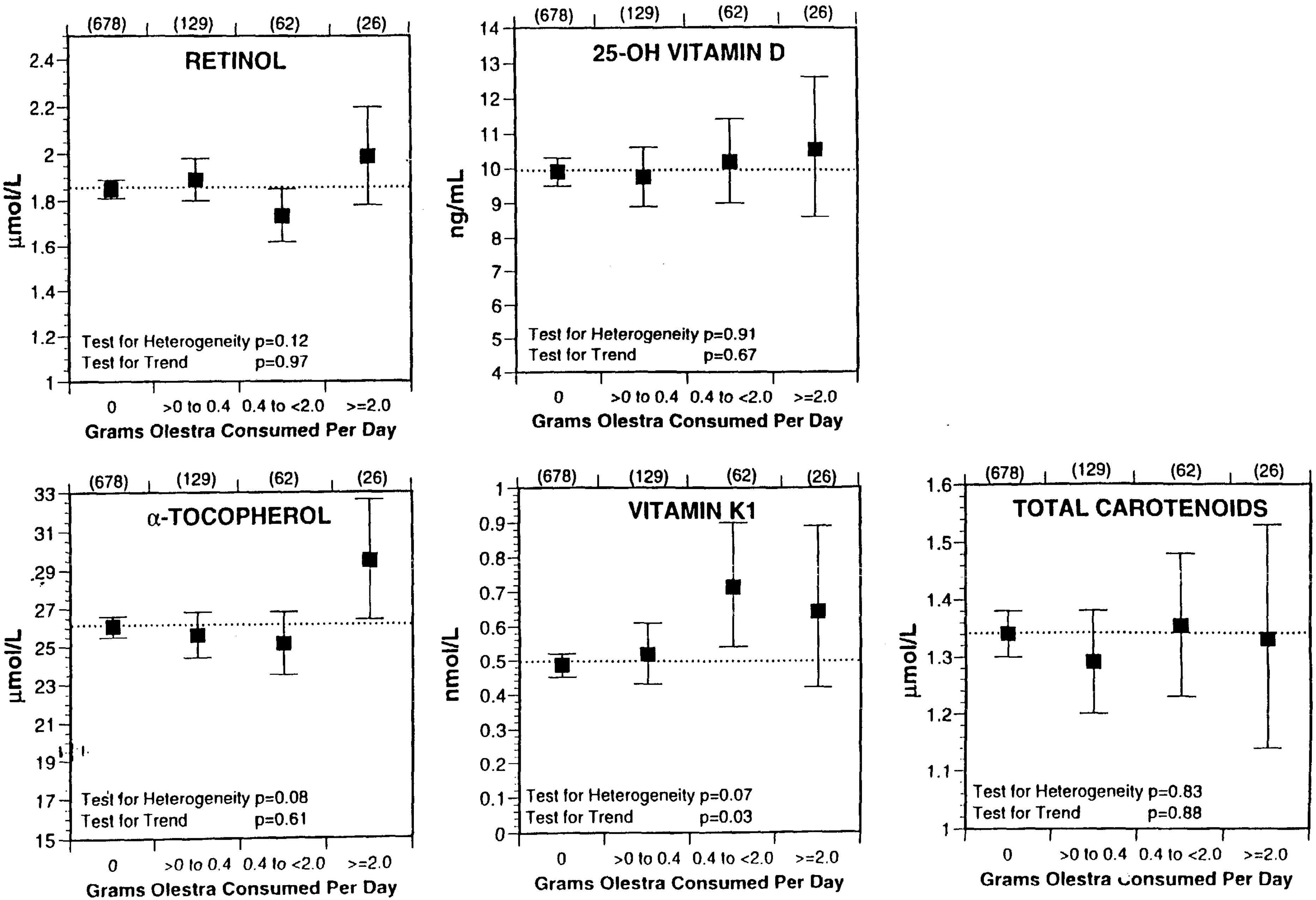
FIGURE 1A.
Adjusted means (±95% CI) from multiple regression models showing serum concentrations of fat-soluble nutrients by level of olestra intake in adults from the Year 1 clinic cross-section (Specific Aim 2). The Olestra Post-Marketing Active Surveillance Study, Indianapolis, IN, 1996-1998.



(Sample sizes for each exposure level are shown in parentheses above each plot. The actual numbers of serum analyses may be slightly lower for some analyses.)

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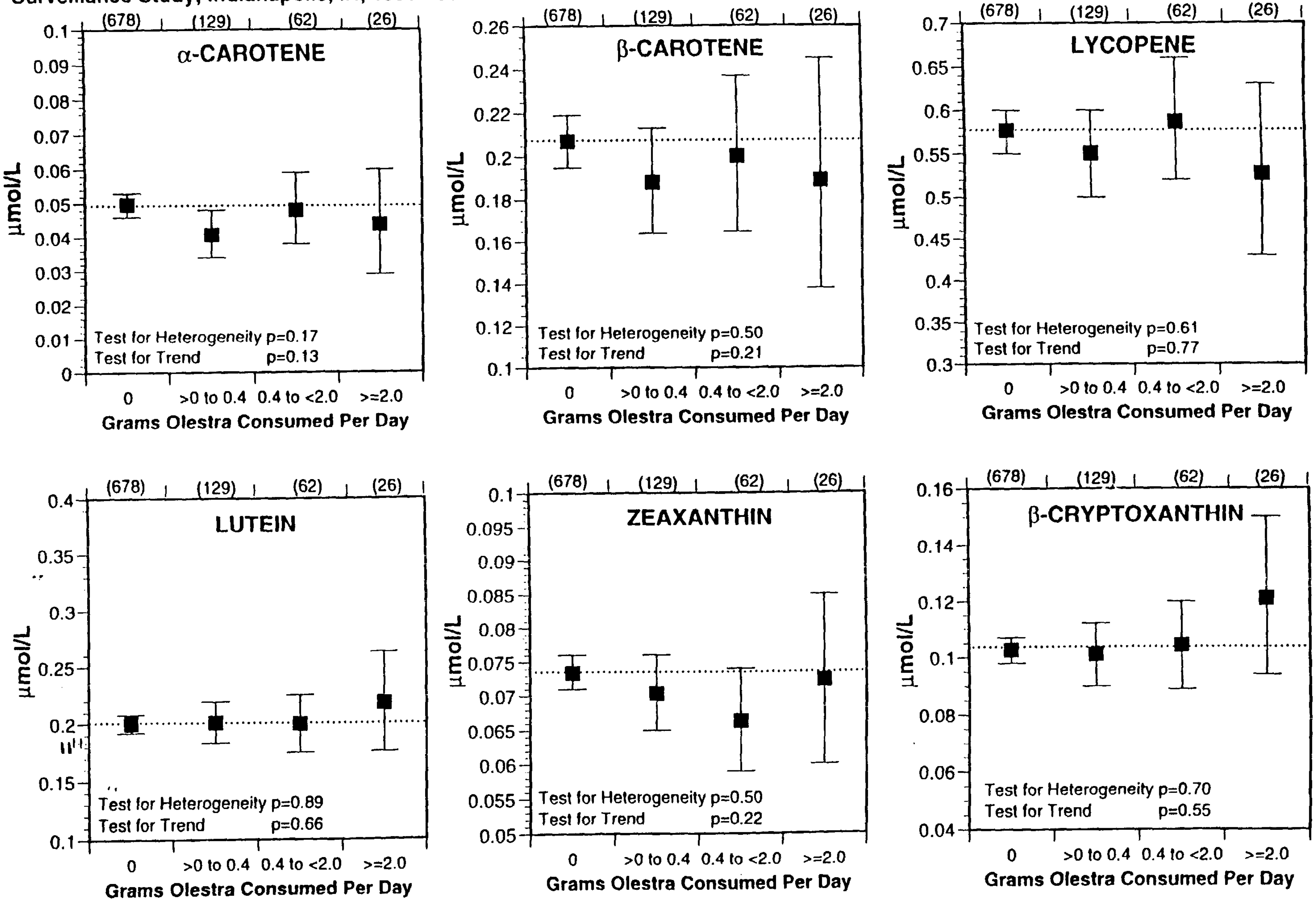
FIGURE 1B.
Adjusted means (±95% CI) from multiple regression models showing serum concentrations of carotenoids concentrations by level of olestra intake in adults from the Year 1 clinic cross-section (Specific Aim 2). The Olestra Post-Marketing Active Surveillance Study, Indianapolis, IN, 1996-1998.



(Sample sizes for each exposure level are shown in parentheses above each plot. The actual numbers of serum analyses may be slightly lower for some analyses.)

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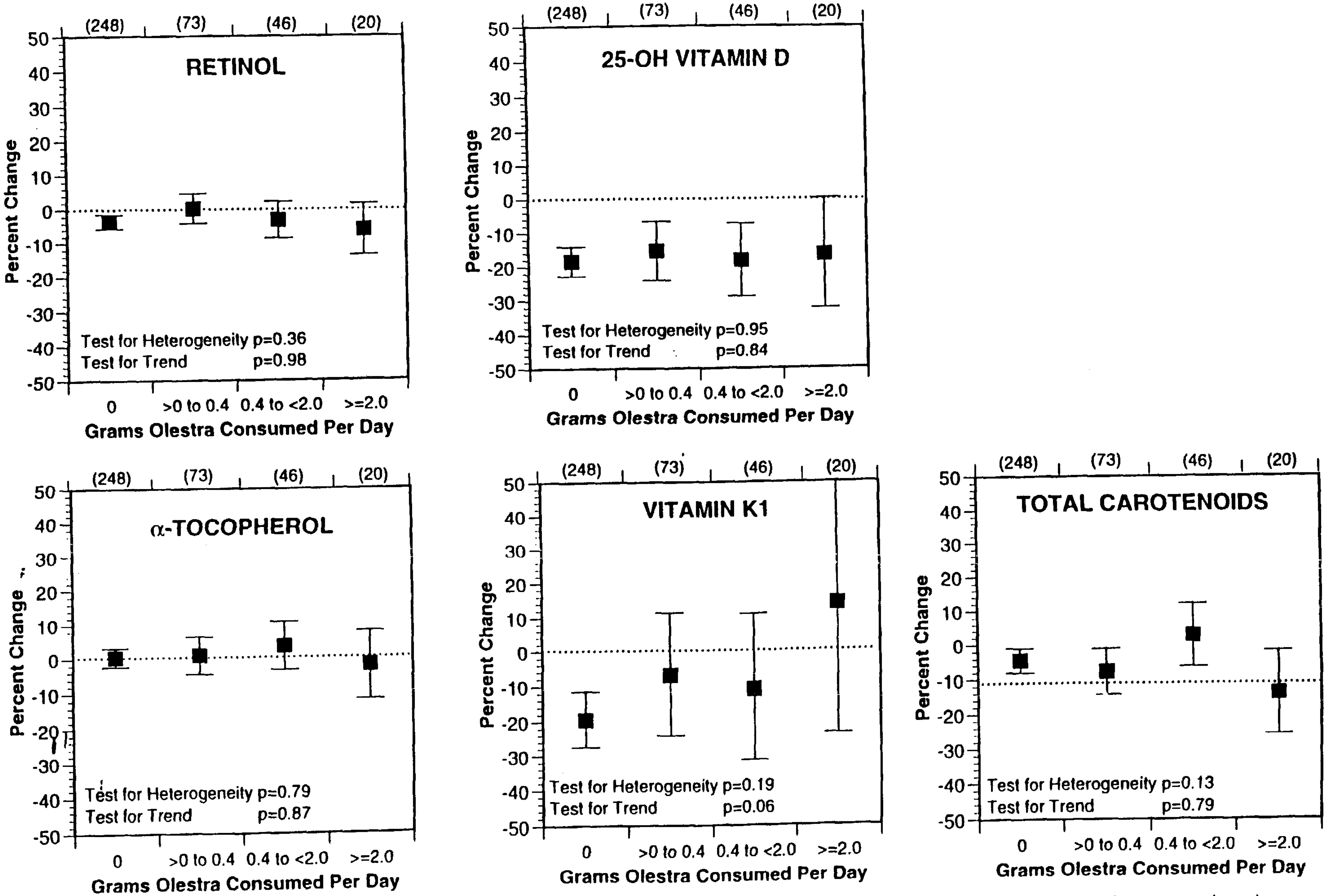
FIGURE 2A.
Adjusted means (±95% CI) from multiple regression models showing percent change in serum concentrations of fat-soluble nutrients serum concentrations by level of olestra intake from Year 0 to Year 1 in adults from the clinic cohort (Specific Aim 3). The Olestra Post-Marketing Active Surveillance Study, Indianapolis, IN, 1996-1998.



(Sample sizes for each exposure level are shown in parentheses above each plot. The actual numbers of serum analyses may be slightly lower for some analyses.)

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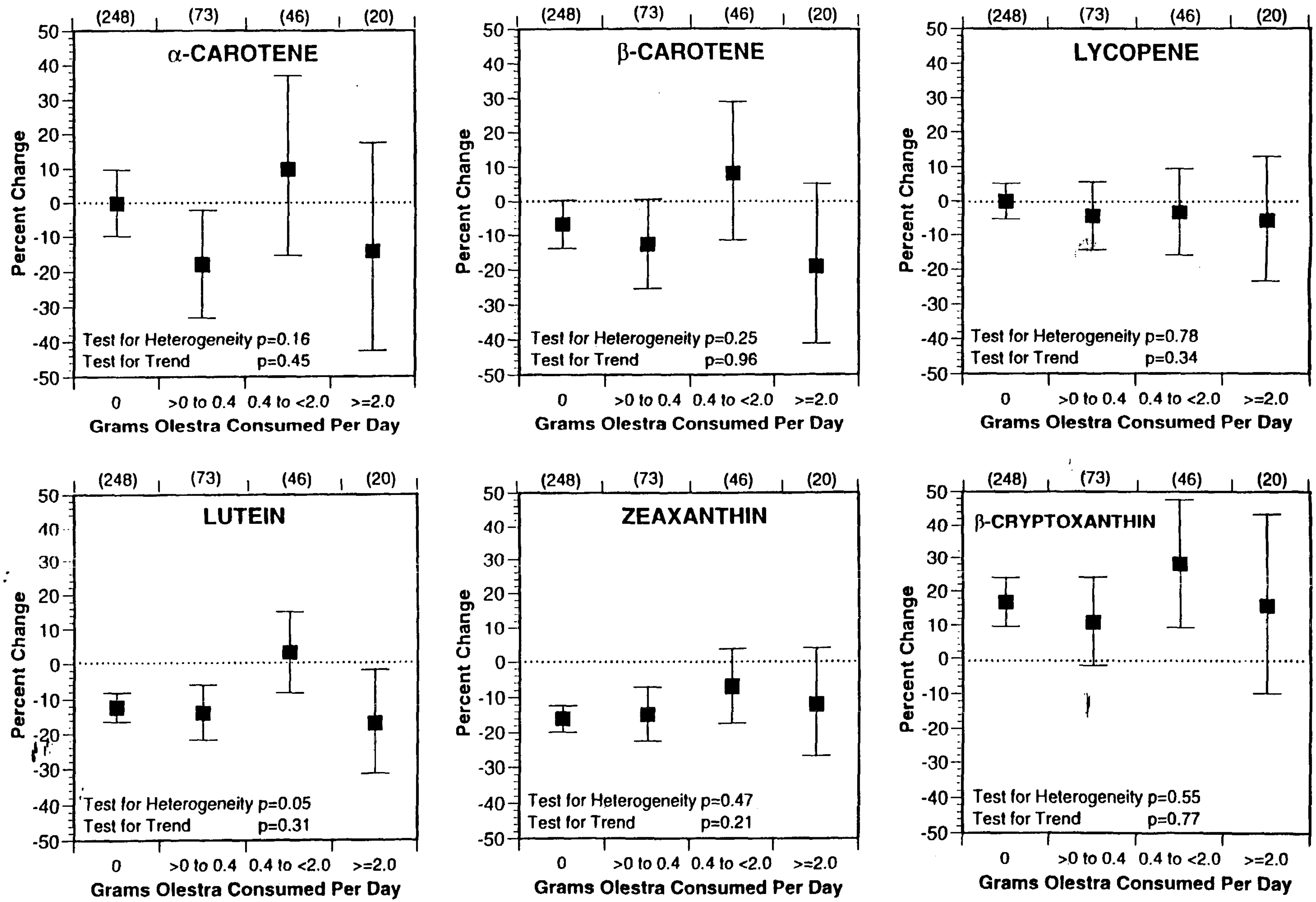
FIGURE 2B.
Adjusted means (±95 CI) from multiple regression models showing percent change in concentrations of serum carotenoids concentrations by level of olestra intake from Year 0 to Year 1 in adults from the clinic cohort (Specific Aim 3). The Olestra Post-Marketing Active Surveillance Study, Indianapolis, IN, 1996-1998.



(Sample sizes for each exposure level are shown in parentheses above each plot. The actual numbers of serum analyses may be slightly lower for some analyses.)